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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,667	10/27/2003	Paul J. Maddon	P0741.70006US00	4456

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/695,667	MADDON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,51-53,55,56,59-61,63-90 and 187-265* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,51-53,55,56,59-61,63-90,187-198,200-236,238-251,253,254,257,258 and 260-265* is/are rejected.

7)☒ Claim(s) *199,237,252,255,256 and 259* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

Note: The Office action mailed August 4, 2009, has been vacated. This Office action is intended to replace the Office action mailed August 4, 2009.

1. The election without traverse filed April 10, 2009, is acknowledged and has been entered.

Applicant has elected the species of invention, wherein the portion of SEQ ID NO: 1 to which the claims are directed is the sequence spanning amino acids 44-750 of SEQ ID NO: 1 and wherein the pH of the composition is 7; however, as noted below, the requirement to elect a species by identifying the pH of the composition to which the claims are directed has been withdrawn.

Notably Applicant has remarked that at least claims 48, 52, 55, 56, 59-61, 63-90, 187-198, 199 (in part), 200-208, 210, 212-236, 237 (in part), 238-250, 252-258,259 (in part), and 260-265 read on the elected species of invention.

2. Claims 48, 51-53, 55, 56, 59-61, 63-90, and 187-265 are pending in the application and currently under prosecution.

Election/Restriction

3. The requirement to elect a species of invention by specifying the pH of the solution to which the claims are directed[1] has been withdrawn in favor of rejoinder.

Priority

4. Applicant's claim under 35 U.S.C. §§ 119 and/or 120 for benefit of the earlier filing date of Application No. 10/395,894, filed March 21, 2003, which claims benefit of U.S. Provisional Application No. 60/335,215, filed October 23, 2001, U.S. Provisional

[1] See the Office action mailed December 10, 2008; see pages 4 and 5, in particular.

Application No. 60/362,747, filed March 7, 2002, and U.S. Provisional Application No. 60/412,618, filed September 20, 2002, is acknowledged.

As before noted, to receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is submitted that at least some the claims do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed because one or more of the priority documents fails to provide written support for the language of the claims. Given the number of claims that are presently under prosecution, it is a serious burden to determine which priority documents provide the necessary written support for which of the claims; nonetheless, it is aptly noted, for example, while claim 78 is directed to the composition of claim 77, wherein the surfactant is Triton X-100, it appears that prior filed Application No. 10/395,894 and any of the provisional applications fail to disclose such a composition. As another example of similar deficiencies of the priority documents, while claim 74 is directed to the composition of claim 48, wherein the composition further comprises a non-naturally occurring free amino acid, it appears that none of Application No. 10/395,894 and any of the provisional applications describes such a composition. Still other deficiencies of Application No. 10/395,894 and any of the provisional applications have been noted, but have not been listed in the interest of brevity.

Furthermore, many of the claims do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are presently rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description.

Thus, it may be that the effective filing date of some of the claims is the filing date of the instant application, namely October 27, 2003; it is however not presently an issue

since the prior art cited in the rejections that follow is prior art even if the claims were to be given the earliest claimed priority.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed February 16, 2007.

Grounds of Objection and Rejection Maintained

Specification

6. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

As before noted, an example of such an improperly demarcated trademark appearing in the specification is BiaCore™ (see, e.g., page 29, line 23).

Notably, although Applicant intended to correct the noted deficiency by appropriately amending the specification, the amendment filed January 31, 2008, was non-compliant with 37 C.F.R. § 1.121 and was not entered[2].

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

[2] Notably, any given section of an amendment (e.g., the amendment to the specification) will not be entered *in part*. So as to be fully compliant, the corrected section of the non-compliant amendment must be resubmitted (**in its entirety**), e.g., the entire "Amendments to the claims" section of applicant's amendment. See 37 CFR § 1.121(h).

7. The objection to the disclosure because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is maintained. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

As before noted, an example of such an impermissible disclosure appearing in the specification is found in paragraph [0177] of the published application[3].

Although Applicant has amended the specification to strike "http://www." from the disclosure in the paragraph at page 38, beginning in line 30, it seems that the specification seeks to describe non-naturally occurring free amino acids as compounds that do not occur in nature but which can be incorporated into a polypeptide chain including, for example, any of those compounds that are described by the website to which the disclosure refers. Although the disclosure, as presently amended, may not contain an active link to the website, the disclosure nonetheless attempts to incorporate essential or non-essential information into the specification by reference to the website.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See M.P.E.P. § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 C.F.R. § 1.57.

Applicant's remark at page 26 of the amendment filed August 20, 2007, is acknowledged.

In response, MPEP 608.01(p) does not provide for incorporation of essential *or* non-essential material by reference to, for example, hyperlinks or other forms of browser-executable code. Essential subject matter may only be incorporated by reference to (1) US patents and pending US applications, or patents or other publications published by a foreign country or a regional patent office, (2) non-patent publications, (3) a US patent or application which itself incorporates material by

[3] U.S. Patent Application Publication No. 2004/0161776 A1.

reference, or (4) a foreign application. Non-essential information may only be incorporated by reference to (1) patents or applications published by the United States, or patents or other publications published by a foreign country or a regional patent office, (2) prior filed, commonly owned US applications, (3) non-patent publications.

It is impermissible that a patent's disclosure incorporate essential or non-essential material by reference to, for example, embedded hyperlinks and/or other forms of browser-executable code (or the contents of the website so identified), because the information contained in the websites or databases to which the hyperlinks or other forms of browser-executable code connect may not be maintained on the Internet for the duration of the patent's term and may not contain the same information after the filing date of an application that was contained in the website or database on or before the filing date of the application. Since the information contained in a website may vary, it is not evident that information contained in a website will always remain useful the practitioner or even applicable to the invention; and information contained in an extinct website cannot possibly be helpful to the practitioner. Furthermore, the validity of a patent containing a reference to a hyperlink or other form of browser-executable code may be reasonably questioned if the website(s) to which the hyperlink(s) connect were relied upon by the patentee(s) to provide sufficient disclosure or description of the invention to meet the requirements of 35 USC § 112, first and second paragraphs. As such, recitation of such references is not permitted.

A hyperlink or other form of browser-executable code may be permitted if the hyperlink or other form of browser-executable code is part of the claimed invention, but in such a case, the Office would disable the hyperlink or other form of browser-executable code.

In general, if the Applicant expects to rely upon the information contained in the websites or databases to provide antecedent basis for the subject matter of claims in a parent application or related applications, and if the material is properly incorporated by reference in the referencing application, Applicant would be required to amend the specification of the referencing application to include the material incorporated by reference to the hyperlink or other forms of browser-executable web, or other non-

permissible sources and to provide a declaration by Applicant or Applicant's representative stating that the amendatory material consists of the same material incorporated by reference in this application. See MPEP § 608.01(p).

If Applicant intends that information contained at the websites to which the disclosures refer be incorporated, Applicant is required to amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by Applicant, or a practitioner representing Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Claim Rejections - 35 U.S.C. § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The rejection of claims 48, 51-53, 55, 56, 59-61, 63-90, 187-195, 197, 198, 200-233, 235, 236, and 238-249, as failing to satisfy the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at page 30 of the amendment filed August 20, 2007, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines

for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a genus of dimers of PSMA proteins that comprise the amino acid sequence of SEQ ID NO: 1 *or a portion thereof*.

The specification discloses at paragraph [0013] of the published application the following:

> In some embodiments the PSMA protein multimers comprise the full-length PSMA protein (SEQ ID NO: 1) or a fragment thereof. In other embodiments the PSMA protein multimer comprises the extracellular portion of PSMA (amino acids 44-750 of SEQ ID NO: 1) or a fragment thereof. In still other embodiments the PSMA protein multimer comprises the amino acids 58-750 of SEQ ID NO: 1 or a fragment thereof. In yet other embodiments the PSMA protein multimer comprises the amino acids 610-750 of SEQ ID NO: 1 or a fragment thereof. The fragments are capable of forming a PSMA multimer that can be used to generate antibodies that recognize PSMA, preferably native PSMA dimer. Typically, the PSMA multimers are homomultimers, meaning that the two or more PSMA molecules are the same. In other embodiments, the PSMA multimers are heteromultimers, whereby at least two of the PSMA proteins are not the same. In still other embodiments the PSMA proteins can be functionally equivalent proteins, whereby the PSMA protein is conservatively substituted.

Then, at paragraph [0166] of the published application, the specification defines the term "PSMA protein" as inclusive of the full-length PSMA protein (provided as SEQ ID NO: 1) or a portion thereof; and at paragraph [0162] the specification describes the PMSA protein, which is capable of forming multimers, particularly dimers, as inclusive of the full-length protein (SEQ ID NO: 1), the extracellular portion of PSMA (amino acids 44-750 of SEQ ID NO: 1), or an alternatively spliced form of PSMA.

The claims however are not limited to compositions comprising dimers composed of PSMA proteins comprising the entirety of the amino acid sequence of SEQ ID NO: 1 or the extracellular portion thereof, but rather to composition comprising dimers composed of PSMA proteins comprising the entirety of the amino acid sequence of SEQ ID NO: 1 or *any* portion thereof.

It is submitted that the extracellular portion of the PSMA protein of SEQ ID NO: 1 is not representative of the claimed genus of PSMA proteins of which the dimer is composed.

This is because the claimed PSMA protein may comprise (or consist of) any portion of SEQ ID NO: 1; and as such members of the claimed genus of proteins have substantially varying structures.

Furthermore, it is submitted that although many PSMA proteins comprising mere portions of SEQ ID NO: 1 might not be expected to be capable of forming the claimed dimer, the skilled artisan cannot immediately envision, recognize or distinguish those that are.

Applicant is again reminded, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes the claimed genus of PSMA protein comprising mere portions of the amino acid sequence of SEQ ID NO: 1, which are capable of forming stable dimers that can be isolated in order to make the claimed compositions thereof. A description of what a material does (or must do), rather than of what it is, does not suffice to describe the claimed invention.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

In this case, the skilled artisan cannot predict whether many of the PSMA proteins comprising mere portions of SEQ ID NO: 1 are capable of forming the claimed dimer.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a list of proteins comprising mere portions of the amino acid sequence of SEQ ID NO: 1, which may have the potential to form a stable dimer that can be isolated so as to permit the production of the claimed composition does not fulfill the written description requirement.

It is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances, such as the claimed PSMA proteins by *only* their functional activity, i.e., the ability to form a stable, isolatable dimer, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding the PSMA proteins comprising mere portions of the amino acid sequence of SEQ ID NO: 1 that are capable of forming stable dimers that can be isolated in order to produce the claimed compositions thereof; without such proteins, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify the PSMA proteins comprising mere portions of the amino acid sequence of SEQ ID NO: 1 that are capable of forming stable dimers that can be isolated in order to produce the claimed compositions thereof by screening a plurality of structurally different PSMA proteins comprising mere portions of the amino acid sequence of SEQ ID NO: 1 to see which are capable of forming the requisite stable dimer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate

written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify the PSMA proteins comprising mere portions of the amino acid sequence of SEQ ID NO: 1, which are capable of forming stable dimers that can be isolated in order to produce the claimed compositions thereof.

However, it seems, at best, the specification only adequately describes a composition comprising a dimer composed of PSMA proteins comprising the whole of the amino acid sequence of SEQ ID NO: 1 or the extracellular portion of the polypeptide of SEQ ID NO: 1 (i.e., amino acids 44-750).

With more particular regard to claims 235 and 236, for example, which are directed to PSMA proteins comprising amino acids 601-750 of SEQ ID NO: 1, it is noted that although the specification discloses that the helical dimerization domain of PSMA consists of amino acids 601-750 of SEQ ID NO: 1[4], it does not appear to provide any factual evidence that reasonably suggests that a polypeptide consisting of only amino acids 601-750 is capable of forming a stable dimer that may be isolated in order to make the claimed compositions. Rather it appears that all of the studies performed in which stable dimers were isolated involved recombinant proteins comprising the entirety of the extracellular domain of the polypeptide of SEQ ID NO: 1.

[4] See, e.g., paragraph [0482] of the published application.

Therefore, in this case, since the claims are so broad, and the disclosure is so comparably limited, it is submitted that any alleged conception has no more specificity than simply a wish to know the identity of any material with that requisite biological properties, which can be used to practice the claimed processes, so as to achieve the claimed objectives or effects.

In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Lastly, since the claims are not necessarily limited to known materials having the properties of the claimed PSMA protein that is capable of forming a dimer, but rather to such material that might be identified, given the bid set forth in the instant disclosure to do so, it is noted that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (Bd. Pat. App. & Int. 1993).

Thus, it is submitted that the instant claims, and the disclosure describing the claimed subject matter, fails to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

New Grounds of Objection

Claim Objections

10. Claims 196-198 and 234-236 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 196-198 and 234-236 are drawn to the composition of claim of 48 or 208, respectively, wherein the sequence of each PSMA protein comprises the sequence of amino acids 44-750 of SEQ ID NO: 1, the sequence of 58-750 of SEQ ID NO: 1, or the

sequence of amino acids 601-750 of SEQ ID NO: 1. However, according to claims 48 and 208 each of PSMA protein of which the isolated dimer of PSMA protein is composed comprises the entirety of the sequence set forth as SEQ ID NO: 1 or, and only in the alternative, a portion thereof. A proper dependent claim must further limit each and every embodiment of the preceding claim. In this case, if the according to claims 48 and 208, each of PSMA protein of which the isolated dimer of PSMA protein is composed comprises the entirety of the sequence set forth as SEQ ID NO: 1, each PSMA protein necessarily comprises the sequence of amino acids 44-750 of SEQ ID NO: 1, the sequence of 58-750 of SEQ ID NO: 1, and the sequence of amino acids 601-750 of SEQ ID NO: 1, such that none of claims 196-198 and 234-236 further limits the subject matter of the preceding claims.

It is suggested that this issue might be remedied by amending claims 196-198 and 234-236 to recite, for example, wherein *said portion thereof* comprises the sequence of amino acids 44-750 of SEQ ID NO: 1, the sequence of 58-750 of SEQ ID NO: 1, or the sequence of amino acids 601-750 of SEQ ID NO: 1.

11. Claims 199 and 237 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 199 and 237 are drawn to the composition of a preceding claim, wherein the sequence of each PSMA protein consists of the sequence of amino acids 44-750 of SEQ ID NO: 1. However, according to each of the preceding claims the PSMA protein of which the isolated dimer of PSMA protein is composed comprises the entirety of the sequence set forth as SEQ ID NO: 1 or, in the alternative, a portion thereof. A proper dependent claim must further limit each and every embodiment of the preceding claim. The PSMA protein that comprises the entirety of the amino acid sequence of SEQ ID NO: 1 cannot consist of amino acids 44-750 of SEQ ID NO: 1.

12. Claims 197, 198, 235, and 236 are objected to as, depending upon interpretation, possibly reading in the alternative on the subject matter of a non-elected species of invention (i.e., a composition comprising a dimer of PSMA proteins, each of which is a protein comprising only a portion of the amino acid sequence of SEQ ID NO: 1, wherein said portions are the sequence of 58-750 of SEQ ID NO: 1 or the sequence of amino acids 601-750 of SEQ ID NO: 1), as opposed to the elected species (i.e., a composition comprising a dimer of PSMA proteins, each of which is a protein comprising 44-750 of SEQ ID NO: 1).

13. Claims 199, 237, 252, 255, 256, and 259 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Notably, it appears that the subject matter encompassed by claims 199, 237, and 259 has not been taught or suggested by the prior art since the prior art does not appear to teach or suggest that a PSMA protein consisting of amino acids 44-750 of SEQ ID NO: 1 (i.e., the extracellular domain of the mature PSMA protein of SEQ ID NO: 1) is capable of forming a stable homodimer in solution. The formation of stable dimers of a recombinant polypeptide consisting of the extracellular domain of PSMA is first described by Schulke et al. (*Proc. Natl. Acad. Sci.* U S A. 2003 Oct 28; **100** (22): 12590-12595) (of record). The specification describes the production of the dimer composed of a recombinant polypeptide consisting of the extracellular domain of PSMA (i.e., amino acids 44-750) in Example 15, e.g., at paragraphs [0386]-[0388] of the published application. The specification discloses that the dimer of the recombinant extracellular domain of PSMA possesses folate hydrolase enzymatic activity (paragraphs [0388]).

New Grounds of Rejection

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 48, 51, 55, 56, 59, 61, 63, 68, 71-73, 77-90, 196-198, 250, 251, 253, 254, and 260 are rejected under 35 U.S.C. 102(b) as being anticipated by Grauer et al. (*Cancer Res.* 1998 Nov 1; **58** (21): 4787-4789), as evidenced by Shulke et al. (*Proc. Natl. Acad. Sci. U S A.* 2003 Oct 28; **100** (22):12590-112595).

As evidenced by Shulke et al., LNCaP cellular lysates comprise an isolated dimer of PSMA protein, which comprises amino acids 44-750 of SEQ ID NO: 1; see entire document (e.g., the abstract).

Grauer et al. teaches a composition comprising lysates of LNCaP cells comprising Triton X-100, magnesium chloride, sodium, and a buffer having a pH of 7.5; see entire document (e.g., the abstract; and page 4787, column 2). Grauer et al. teaches compositions comprising eluents comprising isolated PSMA proteins were prepared by elution in a buffer containing sodium phosphate and 150 mM sodium chloride (page 4787, column 2).

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. Claims 187, 190-193, 208, 209, 212-215, 220, 229, 234, 238, 239, 241, 244, 247-249, 261, and 263-265 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grauer et al. (*Cancer Res.* 1998 Nov 1; **58** (21): 4787-4789), as evidenced by Shulke et al. (*Proc. Natl. Acad. Sci. U S A.* 2003 Oct 28; **100** (22):12590-112595) (of record; cited by Applicant).

As evidenced by Shulke et al., LNCaP cellular lysates comprise an isolated dimer of PSMA protein having the sequence of amino acids 44-750 of SEQ ID NO: 1; see entire document (e.g., the abstract).

Grauer et al. teaches a composition comprising lysates of LNCaP cells comprising Triton X-100, magnesium chloride, sodium, and a buffer having a pH of 7.5; see entire document (e.g., the abstract; and page 4787, column 2).

Grauer et al. however does not expressly teach or suggest the preparation of a lyophilized composition or a kit comprising such composition.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have lyophilized the composition in order to store the composition since lyophilization was commonly used at the time as a means for preparing such compositions for long term storage. Furthermore, it would have *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured a kit comprising the composition since the composition and thus the kit comprising the composition could be used in any of a variety of different application such as, for example, the production of an antibody that specifically binds to a

component of the lysate. Finally, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured a kit comprising the composition further comprising a vial to store composition, a diluent to resuspend the lyophilized composition, and/or a syringe, if the vial is comprised of a septum, since the syringe could then be used to penetrate the septum in order to resuspend the lyophilized composition using the diluent. In any event, one ordinarily skilled in the art at the time the invention was made would have been motivated to manufacture such a kit since such kits and their components provide convenience and ease of use, and so are routinely used in the relevant arts.

19. Claims 48, 51-53, 55, 56, 59, 61, 63, 71, 72, 74, 77-90, 187, 189-193, 196-198, 207-215, 229, 234-236, 238-244, and 247-249 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Jan; **93**: 749-753) (of record) and Tiffany et al. (*Prostate.* 199; **39**: 28-35) (of record), as evidenced by Slusher et al. (*J. Biol. Chem.* 1990 Dec 5; **265** (34): 21297-21301), Robinson et al. (*J. Biol. Chem.* 1987 Oct 25; **262** (30): 14498-14506) (of record), and Schulke et al. (*Proc. Natl. Acad. Sci. USA.* 2003 Oct 28; **100** (22): 12590-12595) (of record; cited by Applicant).

Carter et al. teaches a composition of isolated PSMA protein that has enzymatic activity with the substrate and pharmacologic properties of the *N*-acetylated α-linked acidic dipeptidase (NAALADase); see, entire document (e.g., the abstract; page 751, Table 1).

Carter et al. teaches the enzymatic assay was performed by first solubilizing cells expressing PSMA protein in a solution containing 50 mM Tris-HCl buffer (pH 7.4 at 37 °C) and 0.5% Triton X-100. Carter et al. discloses that a volume of the lysates containing 20-100 mg of protein was assayed for NAAG-hydrolyzing activity according to the protocol described by Slusher et al (page 750, column 1); and according to Slusher et al. the assay used is described by Robinson et al., except for the inclusion in the assay of 1 mM $CoCl_2$ (page 21301, column 1).

According to Robinson et al., the assay was performed in a solution comprising 50 mM Tris-HCl buffer (pH 7.4) and a dipeptide substrate that is cleaved by the protein to form a free amino acid (page 14499, column 2). Furthermore, according to Robinson et al., the assay is free of chelating agents.

As evidenced by Schulke et al., mature PSMA occurs as a non-covalent homodimer of PSMA proteins in a native conformation under non-denaturing conditions and that dimerization is required for enzymatic activity; see entire document (e.g., the abstract).

Therefore, as evidenced by Schulke et al., Carter et al. teaches a composition comprising an isolated PSMA protein, at least a portion of which formed dimers, because otherwise the preparation of isolated PSMA protein would have lacked enzymatic activity.

Carter et al. teaches the pH of the solution comprising the isolated PSMA dimer is 7.4. Carter et al. does not teach or expressly suggest that the pH of the solution may be varied, or that more particularly the pH could be 6.5, 7, or 7.5; nevertheless, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to vary the pH of the solution within a narrow range of 7.4 in order to determine the optimal assay conditions or to study the effect of pH on the activity of the protein. The variance and optimization of the pH solution would be understood to be important, especially if any of the other enzymatic activities of PSMA were to be assayed. Applicant is therefore reminded that although obviousness can be established by modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is submitted that there is indeed some teaching, suggestion, or motivation to vary the pH of the solution, which is found both in the reference itself and in the knowledge generally available to one of ordinary skill in the art.

Carter et al. does not teach the inclusion of a salt; nonetheless, Tiffany et al. teaches the effect of including $CoCl_2$ or NaCl in an assay of PSMA enzymatic activity indicated that the activity of the protein is both stimulated by the chloride anion and the cobalt cation; see, e.g., page 30, column 2; and page 31, column 2. Additionally, Tiffany et al. found that the presence of a chelator (i.e., EDTA) resulted in the inhibition of the activity of the protein in the assay, which suggests that the enzyme is stimulated by the presence of divalent metal ions; see e.g., page 31, column 2. In light of such disclosures it is submitted that it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have, not only the pH of the solution, but its chemical make-up in order to determine the optimal concentrations of chloride salts and divalent metal cations in the assay of the enzymatic activities of PSMA.

Nonetheless, inasmuch as it would have been obvious to use chromatography to purify PSMA, it is further submitted that the production of the claimed composition comprising a salt in the concentration range of 100 mM to 300 mM (or more particularly at a concentration of 150 mM) would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention, as such a composition could have been readily made in the process of purifying the protein by such means.

It is of course recognized then that the chemical make-up of any composition of PSMA will largely depend upon the application for which, or by which the composition is made.

Such minor or insignificant differences however should not be considered non-obvious, particularly since the claimed composition may be made by or used in so many different applications.

For example, the claimed composition need not have enzymatic activity. In fact, the claimed composition may be lyophilized (see claim 208, for example); and lyophilization is generally understood to produce a form of a composition that is suitable for long-term storage of the composition, which must be resuspended before any further use. As such, it is apparent that the chemical make-up of the solution might best be

one that sustains the integrity of the protein during storage[5]; and if so, it is submitted that the inclusion of at least one salt in the requisite range would be desirable.

As for claims 187 and 190-192, drawn to a kit, such a kit would have been prima facie obvious to one ordinarily skilled in the art at the time of the invention since it would have been immediately recognized that the claimed composition of the which the kit is comprised could find any number of uses in laboratories. It was and continues to be common practice to manufacture kits comprising reagents need for experimentation since such kits provide a convenient source of those reagents.

Note: For clarity with regard to claims 200-203, which are not included in this rejection, because Carter et al. does not teach the specific activity of the preparation of isolated PSMA protein, the number of moles of the protein present in the volume of the preparation used in the assay cannot be determined; as such, although the assay of Carter et al. contained 1 mM metal ion (Co^{2+}), it is believed that the number of molar equivalents of the metal ion, relative to the number of moles of PSMA protein, cannot be determined.

20. Claims 250, 257, and 258 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grauer et al. (*Cancer Res.* 1998 Nov 1; **58** (21): 4787-4789), as evidenced by Shulke et al. (*Proc. Natl. Acad. Sci. U S A.* 2003 Oct 28; **100** (22):12590-112595), as applied to claims 187, 190-193, 208, 209, 212-215, 220, 229, 234, 238, 239, 241, 244, 247-249, 261, and 263-265 above, and further in view of Hong et al. (*J. Immunol. Methods.* 1989 Jun 21; **120** (2): 151-157).

As evidenced by Shulke et al., Grauer et al. teaches that which is set forth in the above rejection of claims 187, 190-193, 208, 209, 212-215, 220, 229, 234, 238, 239, 241, 244, 247-249, 261, and 263-265 under 35 U.S.C. 103(a).

Grauer et al. does not expressly teach or suggest a compostion comprising the protein and an adjuvant, such as alum or complete or incomplete Freund's adjuvant.

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[5] As an example of the experimentation that might be performed to identify components of a solution for storing an enzyme, see Martin (*Thromb. Diath. Haemorrh.* 1975 Jun 30; **33** (3): 586-596).

Hong et al. teaches the production of polyclonal and monoclonal antibodies in mice using immunogens comprising different adjuvants, including alum, complete Freund's adjuvant and incomplete Freund's adjuvant.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured a kit comprising the claimed composition since the composition and thus the kit comprising the composition could be used in any of a variety of different application such as, for example, the production of an antibody that specifically binds to a component of the lysate. Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured a kit comprising the composition, which further comprises an adjuvant, a vial to store composition, a diluent to resuspend the lyophilized composition, and/or a syringe, if the vial is comprised of a septum, since the syringe could then be used to penetrate the septum in order to resuspend the lyophilized composition using the diluent. One ordinarily skilled in the art at the time the invention was made would have been motivated to manufacture such a kit since the kit could be used to make an antibody that binds to the protein, and besides such kits and their components provide convenience and ease of use, and so are routinely used in the relevant arts.

21. Claims 262-265 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grauer et al. (*Cancer Res.* 1998 Nov 1; **58** (21): 4787-4789), as evidenced by Shulke et al. (*Proc. Natl. Acad. Sci. U S A.* 2003 Oct 28; **100** (22):12590-112595), in view of Hong et al. (*J. Immunol. Methods.* 1989 Jun 21; **120** (2): 151-157).

As evidenced by Shulke et al., Grauer et al. teaches that which is set forth in the above rejection of claims 187, 190-193, 208, 209, 212-215, 220, 229, 234, 238, 239, 241, 244, 247-249, 261, and 263-265 under 35 U.S.C. 103(a).

Grauer et al. does not expressly teach or suggest a kit comprising the claimed composition comprising the isolated dimer of PSMA and an adjuvant, such as alum or complete or incomplete Freund's adjuvant.

Hong et al. teaches the production of polyclonal and monoclonal antibodies in mice using immunogens comprising different adjuvants, including alum.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured a kit comprising the claimed composition since the composition and thus the kit comprising the composition could be used in any of a variety of different application such as, for example, the production of an antibody that specifically binds to a component of the lysate. Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured a kit comprising the composition, which further comprises an adjuvant, a vial to store composition, a diluent to resuspend the lyophilized composition, and/or a syringe, if the vial is comprised of a septum, since the syringe could then be used to penetrate the septum in order to resuspend the lyophilized composition using the diluent. One ordinarily skilled in the art at the time the invention was made would have been motivated to manufacture such a kit since the kit could be used to make an antibody that binds to the protein, and besides such kits and their components provide convenience and ease of use, and so are routinely used in the relevant arts.

Conclusion

22. No claim is allowed.

23. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Meighan et al. (*J. Protein Chem.* 2003 May; **22** (4): 317-326) teaches the production of a recombinant protein consisting of the extracellular domain of PSMA and an epitope tag.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
October 24, 2009